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Energy balance after bariatric surgery

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Chapter 4

**Ileal transposition in rats reduces resting metabolic rate
irrespective of nutritional state or macronutrient
composition of the diet**

Abstract

Background: Ileal transposition (IT) allows the direct study of the effects of ileal overstimulation on energy balance regulation, without the confounds of gastric restriction or foregut exclusion. While IT causes reduced body weight and food intake, it is still largely unclear whether and how the different components of energy expenditure (EE) are altered by IT and if macronutrient composition of the diet can influence these effects.

Objective: To determine the effects of the changes in EE and its components as well as the different macronutrients on weight loss after IT.

Methods: Adult male Lewis rats were maintained on one of three different isocaloric liquid diets: high fat (HF), high protein (HP) and high carbohydrate (HC) then underwent either IT or sham surgery. Daily food intake and body weight were recorded. After recovery rats were subjected to a 3-day EE measurement: fasting, limited intake and ad libitum days. EE components and energy budget were calculated.

Results: IT caused reduction in food intake, body weight and fat mass. Total daily EE and its components were decreased but the effects of surgery persisted only on resting metabolic rate irrespective of macronutrient composition or nutrition state, when lean body mass was used as a co-variate.

Conclusions: Our data demonstrate that the observed weight loss following IT explains the reduced EE and the decrease of its components with ingestion-related energy expenditure (IEE) being the only exception. HP diet was the most effective in reducing body weight and in increasing IEE compared to HC and HF.

Introduction

Overweight and obese individuals have an increased risk of developing a cluster of derangement collectively mentioned the metabolic syndrome (McGuire et al 2011), which can develop into life threatening diseases like type 2 diabetes (Dixon et al 2011), cardiovascular diseases (Ghandarana et al 2012) and cancer (Azvolinsky 2016). To reduce the burden on our health care system (Finkelstein et al 2009), even modest weight loss can significantly reduce morbidity and mortality of the obese (Khaylis et al 2010, Stefater et al 2012). However, public and private health advice to reduce or alter food intake and increase exercise/physical activity has not prevented the obesity epidemic from accelerating (Kraschnewski et al 2010, Weiss et al 2007). Medical programs developed several noninvasive options to lose and maintain adequate body weight, which were not always successful mainly because the weight loss is hard to sustain (Khaylis et al 2010, Stefater et al 2012).

In the last few decades however, bariatric surgery emerged offering the most effective and long-term weight loss know today. Ileal transposition is one of these surgeries resulting in weight loss (Koopmans et al 1984, Ramzy et al 2013) without causing gross malabsorption (Strader 2005) or altering the normal intestinal fat absorption (Chelikani et al 2010). Since IT does not involve gastric restriction, or foregut exclusion the reduction of food intake and body weight are presumably due to ileal over-stimulation. A well-known mechanism is the so-called “ileal brake”, which is a complex negative feedback mechanism of the gastrointestinal tract, originating from the stimulated ileal segment, resulting in the activation of neural and endocrine mechanisms that in turn lead to delayed gastric emptying, gastrointestinal transit, secretion of gut hormones, and satiety (Barreto et al 2018, Maljaars et al 2008, Masclee et al 2010,).

Several studies have shown a reduction in resting metabolic rate (RMR) following Roux-en Y gastric bypass (RYGB) surgery (Mirahmadian et al 2018, Miras et al 2013,

Tamboli et al 2010) which may depend on the level of weight loss (de Cleve et al 2018, Miras et al 2013, Moehlecke et al 2015). Effects of RYGB on total daily energy expenditure are variable (Rabl et al 2014, Schmidt et al 2015, Zheng et al 2009), and may depend on the level of physical activity (Mirahmadian et al 2018, Thivel et al 2013). Diet-induced thermogenesis (DIT) was found mostly increased post-operatively to RYGB surgery, which appeared to coincide with successful weight loss (Faria et al 2012, Miras et al 2013). To our knowledge, such studies on the effect of IT on energy expenditure, and the different components herein are lacking. For that reason, we investigated the different components of energy expenditure (i.e., RMR, IEE, and non-exercise activity thermogenesis, NEAT) and related energy balance parameters following IT (IT+) in rats compared to rats undergoing a sham operation (IT-). Since the macronutrient composition of the diet is a crucial factor in energy balance regulation too (Hall 2017), we considered the effects of IT in rats that were fed a high fat (HF), high protein (HP) or high carbohydrate (HC) diet. We have previously shown that rats undergoing IT have most profound reductions in food intake and body weight when they are feeding a HP diet, while rats on the HC and HF diets regained more weight following IT (unpublished observations). However, information on metabolism is lacking, thus we investigated whether dietary macronutrient composition also had an effect on the potential outcomes of IT on components of EE.

Methods

Animals

Forty-four male Lewis rats (mean weight 310 g) were housed individually in plastic cylindrical cages (diameter: 33 cm height: 50 cm) with rat chow (Labdiet®, PROLAB RMH2500 Rodent diet, PMI Nutrition International, LLC, MO, USA) and water ad libitum under artificial lighting (6am – 6pm) at room temperature. After 6 days

of acclimatization rats were separated into three weight matched groups and maintained on high fat (HF), high protein (HP) and high carbohydrate (HC) liquid diet which they could freely ingest daily between 4pm (i.e., 2 hrs. before lights off) till 9 am (i.e., 3 hrs. after lights on) next day. Food jars were weighted at the beginning and at the termination of feeding, and food intake was calculated by taking the difference between the weights of the freshly provided jars and those at the end of the daily feeding cycle. Rats were weighted daily at 3.30 pm before food was presented. After 8 days on the diets rats were matched for body weight and body weight gain and divided into two surgical groups: ileal transposition (IT+, n=6-8 per diet group) and control surgery (IT-, n=7-8 per diet group). All the protocols followed the Canadian Animal Care guidelines and were approved by the University of Calgary, Animal Resource Care Centre.

Diets

Rats were maintained on one of the three liquid diets, which consisted of 1) Ensure Plus (Abbott Canada Saint-Laurent, Québec, Canada), 2) Resource Beneprotein powder (Novartis Medical Nutrition, USA), 3), Intralipid 20% (Fresenius Kabi Clayton L.P., Clayton, NC) and Maltlevol liquid vitamin mix (Carter-Horner Corp Mississauga ON, Canada) and water mixed at different quantities. The mixing yielded three equicaloric diets of each 4.184kJ/gram, consisting of carbohydrate/protein/fat energy percentages of 50/25/25 (high carbohydrate diet), 25/50/25 (high protein diet), or 25/25/50 (high fat diet). Detailed recipe can be found in chapter 3.

Surgery

After an overnight fast rats were anaesthetized with ether. The skin and then the muscle layer of the abdomen were cut at the midline exposing the gastrointestinal tract. The small intestine was then transected at three locations: 1) at the level of the duodenum

1 to 2 cm below the common bile and pancreatic duct, 2) at the level of the ileum at 10 cm from the ileocecal valve, and 3) at the level of the ileum 10 cm above this transection, creating an isolated 10 cm ileal segment.

Ileal transposition surgery: the 10 cm ileal segment was connected (using 6-0 Ethicon silk sutures) to the transected ends of the duodenum in the original direction of flow keeping its mesenteric blood supply and innervation intact. The remaining ends of the ileum were sutured together, resulting in a gastrointestinal tract which had its original length without any excluded parts.

Control surgery. All transactions were re-anastomosed in their original order, returning the intestine to its continuity.

Rats were immediately returned to their home cages with a heating pillow underneath the cage to provide thermoregulatory help after surgery. Analgesic care was given in the form of Gentamicin (i.p. 37 µl/100 g body weight, 40 mg/ml, Sabex Inc Boucherville QC) and Torbugesic (Butorphanol Tartrate; i.p. 0.2 mg/100 g body weight, 10 mg/ml, Wyeth Canada Guelph, ON). Rats did not have access to food for 24 hours after surgery, but water was freely available. More detailed description of surgical procedures can be found elsewhere (Chapter 2).

Energy expenditure measurement

Starting on the 33rd day after surgery, rats underwent indirect calorimetry measurement for analysis of energy expenditure (EE) using an Oxymax Analyzing System (Columbus Instruments, Columbus, OH) over the course of 3 consecutive days, for 23 hrs. per day. To this end, they were put in air-tight cages (diameter: 33 cm height: 50 cm), with wood shavings from their home cage, and with an airflow of 2.5 l/min. Every 10 min, air samples were taken from the outgoing airflow, and after drying were analyzed for

O₂ and CO₂ concentrations, and these levels were compared to the O₂ and CO₂ levels measured in the dried samples of inflowing air. Differences in these concentrations yielded the rat's O₂ consumption and CO₂ production. O₂ and CO₂ sensors were calibrated daily with a standard gas mixture of 20.55% O₂ and 0.490% CO₂. EE was assessed on the basis of the equation of Lusk (Lusk G. The elements of the science of nutrition) and Ferranninni (Ferrannini 1988).

Before the start of indirect calorimetry, rats spent one day with ad libitum food available from 4:00 pm to 9:00 am to habituate them to the indirect calorimetry cages. At the start of indirect calorimetry, rats first underwent a day of fasting. Consequently, the measurement on fasting day established a baseline or minimum of total energy expenditure (TEE) and its components, resting metabolic rate (RMR, calculated by the average of the four lowest EE readings multiplied by 144, to convert the 10 min readings to RMR for the whole day) and non-exercise activity thermogenesis (NEAT=TEE-RMR) under non-feeding condition. During the second day (limited intake day), rats received a food jar filled with exactly 251 kJ of their habitual diet, which was slightly below their normal intake. This limited and standardized intake allowed us to assess ingestion-related energy expenditure (IEE in other articles often called diet-induced thermogenesis, DIT), by calculating the excess EE on the limited intake above the level of EE on the fasting day. Expressing this as a percentage of the known daily energy intake (251 kJ) is termed the specific dynamic action (SDA) of ingested nutrients for each rat (Lusk 1924, McCue 2006) This calculated SDA for each rat is an approximation of the energy expenditure effect of any amount of energy ingested (Lusk 1924), and thus also could be used to approximate IEE under ad libitum condition, which took place during the third day of indirect calorimetry. On the third day, TEE, RMR (i.e., lowest running mean), IEE (based on SDA of the limited intake day) and NEAT (i.e., TEE- [RMR+IEE]) were calculated.

Energy budget was calculated by subtracting TEE from TEI on the limited and ad libitum intake day.

Energy budget calculation

Because daily total energy intake (TEI) and TEE were exactly calculated on the ad libitum day, this allowed us to calculate an energy budget by subtracting TEE from TEI.

Carcass analysis.

Rats were euthanized by decapitation under ether anesthesia between days 49 and 52 after surgery. Visceral organs and skin were removed from the carcass. Body fat was estimated by weighing all abdominal and subcutaneous tissue depots. These values were recalculated to estimate adipose tissue content, which – subtracted from body weight - yielded and estimation for lean body mass (LBM).

Statistical analysis

Comparisons between surgical groups, diet groups, and interactions were done for energy intake, body weight, energy expenditure and calculated components hereof with two-way ANOVA (with diet and surgery as factors), and post-hoc with Tukey's pairwise multiple comparison. Energy expenditure components was analyzed with ANCOVAs (with lean body mass assessed at the end of the experiment, and total body weight at the end of an indirect calorimetry day as co-variates of body size) to assess differences of mass-specific metabolic rates (Fernández-Verdejo et al., 2019). Data is presented as mean \pm SEM, and p values less than 0.05 were considered significant. One animal was excluded for ANCOVA analysis because the LBM was measured incorrectly.

Results

Body weight and food intake

After surgery, IT+ rats lost significantly more weight ($F_{1,38}=9.290$, $p=0.004$) and had longer time before their body weight started to increase again ($F_{1,38}=48.669$, $p<0.0001$), than rats underwent IT-. This resulted in an overall smaller weight gain between pre-surgery average (6 days) and the 30th day (Figure 1A) in the IT+ groups than in IT- ($F_{1,38}=43.338$, $p<0.0001$).

In the week prior energy expenditure measurements body weight ($F_{1,38}=33.015$, $p<0.0001$, Figure 1B) and energy intake ($F_{1,38}=16.301$, $p<0.0001$, Figure 1C) were significantly lower in the IT+ groups than in the IT-. There was also a general effect of diet on both body weight ($F_{2,38}=3.252$, $p<0.05$) and energy intake ($F_{2,38}=4.872$, $p=0.013$). The HC groups weighted more than the HP groups did ($p=0.017$) and it tended to be heavier than the HF diet group ($p=0.11$) but consumed less energy compared to the HF group ($p=0.029$). The HP diet groups also consumed less energy compared to the HF diet groups ($p=0.005$).

At the end of the study, carcass dissection revealed that fat mass (FM, figure 1D) was affected by surgery ($F_{1,37}=29.197$ $p<0.01$), with all IT+ groups having less fat mass ($p<0.01$) than IT- groups. There was also a diet effect ($F_{2,37}=5.714$ $p<0.01$), which was mainly due to HP fed rats having significantly lower fat mass than HF fed rats ($p<0.01$). According to Levene's test data of LBM was not normally distributed. After log-transformation, data became normally distributed, but yielded no significant effect of surgery or diet.

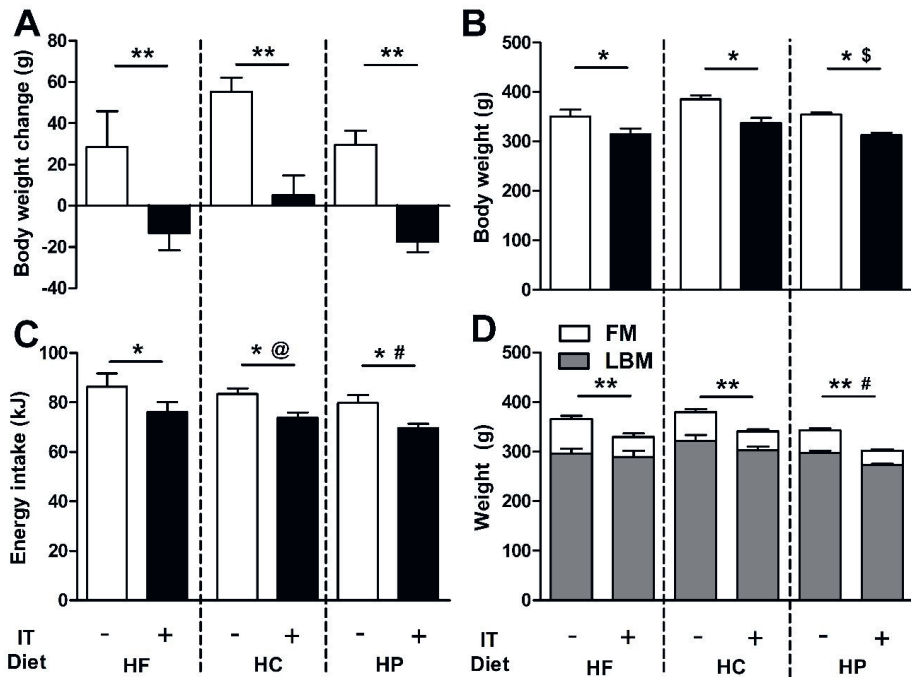


Figure 1. Panel A: Body weight change during the first thirty-day period after ileal transposition (IT+) and control surgery (IT-) in rats feeding a high fat (HF), high carbohydrate (HC), or high protein (HP). Panel B: average body weight and panel C: energy intake over the 7-day period before the energy expenditure measurements. Panel D: Body fat mass and lean body mass after sacrifice around day 50 after IT. Levels of significance by IT are depicted by * ($p < 0.05$), ** ($p < 0.01$), levels of significance by diet are depicted by \$; $p < 0.05$, for difference between HP and HC, #: $p < 0.05$, for difference between HP and HF, and @: $p < 0.05$, for difference between HF and HC. For figure 1D this significant difference is based on FM.

Energy expenditure

Fasting day

Energy expenditure characteristics in fasted, food limited and ad libitum conditions are shown in Figure 2. During fasting conditions (Figure 2A), IT+ rats had lower total energy expenditure (TEE_{fast} ; $F_{1,38}=17.037$, $p<0.001$), resting metabolic rate (RMR_{fast} ; $F_{1,38}=11.374$, $p<0.01$) and non-exercise activity thermogenesis ($NEAT_{fast}$; $F_{1,38}=10.034$, $p=0.01$) compared to IT- rats.

After using an ANCOVA with lean body mass as co-variate, the effect of surgery persisted, with lower levels of TEE_{fast} ($F_{1,37}=11.917$, $p=0.001$), RMR_{fast} ($F_{1,37}=7.162$, $p<0.05$) and $NEAT_{fast}$ ($F_{1,37}=7.695$, $p<0.01$) in IT+ rats versus IT- rats. When using fasting body weight as co-variate, an interaction between surgery and diet was found ($F_{2,37}=3.381$, $p=0.031$). No diet effect was seen on any of these energy expenditure components, both without and with body weight and lean body mass as covariates.

Limited intake day:

During the limited intake day (Figure 2B), IT+ rats had lower TEE_{lim} ($F_{1,38}=12.788$, $p=0.001$), RMR_{lim} ($F_{1,38}=11.987$, $p=0.001$), and $NEAT_{lim}$ ($F_{1,38}=8.629$, $p<0.01$) compared to IT- rats. Specific Dynamic Action (SDA) was not affected by surgery, but was affected by diet ($F_{2,38}=8.005$, $p=0.001$), post-hoc analysis showed that this difference was due to significant higher levels found in the HP diet group versus the HC group ($p=0.001$) and HF group ($p=0.006$). This difference in SDA resulted in a diet effect on IEE_{lim} ($F_{2,38}=7.012$, $p<0.01$), with higher levels of IEE_{lim} in the HP diet group relative to the HC ($p=0.003$) and HF ($p=0.017$) diet group.

ANCOVA with lean body mass as co-variate -yielded effects of surgery on TEE_{lim} ($F_{1,37}=8.281$, $p<0.01$), RMR_{lim} ($F_{1,37}=8.201$, $p<0.01$) and $NEAT_{lim}$ ($F_{1,37}=5.586$, $p<0.05$). ANCOVA with total body weight after the limited intake day as co-variate did not yield significant differences of surgery on any of the energy expenditure components. The effect of diet on SDA remained with lean body mass ($F_{2,37}=8.700$, $p<0.001$) and body weight ($F_{2,37}=10.528$, $p<0.0001$) as co-variables. Likewise, diet affected IEE_{lim} with lean body mass ($F_{2,37}=7.641$, $p=0.002$) and

body weight ($F_{2,37}=9.329$, $p<0.001$) as covariates with the highest levels found in the HP diet group, relative to other diet groups.

Ad libitum day:

During the ad libitum day (Figure 2C), surgery affected TEE_{adlib} and RMR_{adlib} ($F_{1,38}=13.577$, $p<0.001$), with generally lower levels in the IT+ group compared to the IT- group. Additionally, RMR_{adlib} showed a diet effect ($F_{2,37}=3.634$, $p=0.036$). Post-hoc analysis showed that the HP diet group had higher levels compared to the HF diet group ($p=0.013$). TEE_{adlib} , $NEAT_{adlib}$ and IEE_{adlib} , were not affected by surgery or diet.

When using LBM as covariate the effect of surgery ($F_{1,37}=9.776$ $p<0.01$) and diet ($F_{2,37}=3.445$, $p=0.042$) on RMR_{adlib} remained. The effect of surgery on TEE_{adlib} disappeared, however a diet effect appeared on IEE ($F_{2,37}=3.749$ $p=0.033$), where the HP diet group had higher values compared to the HC diet group.

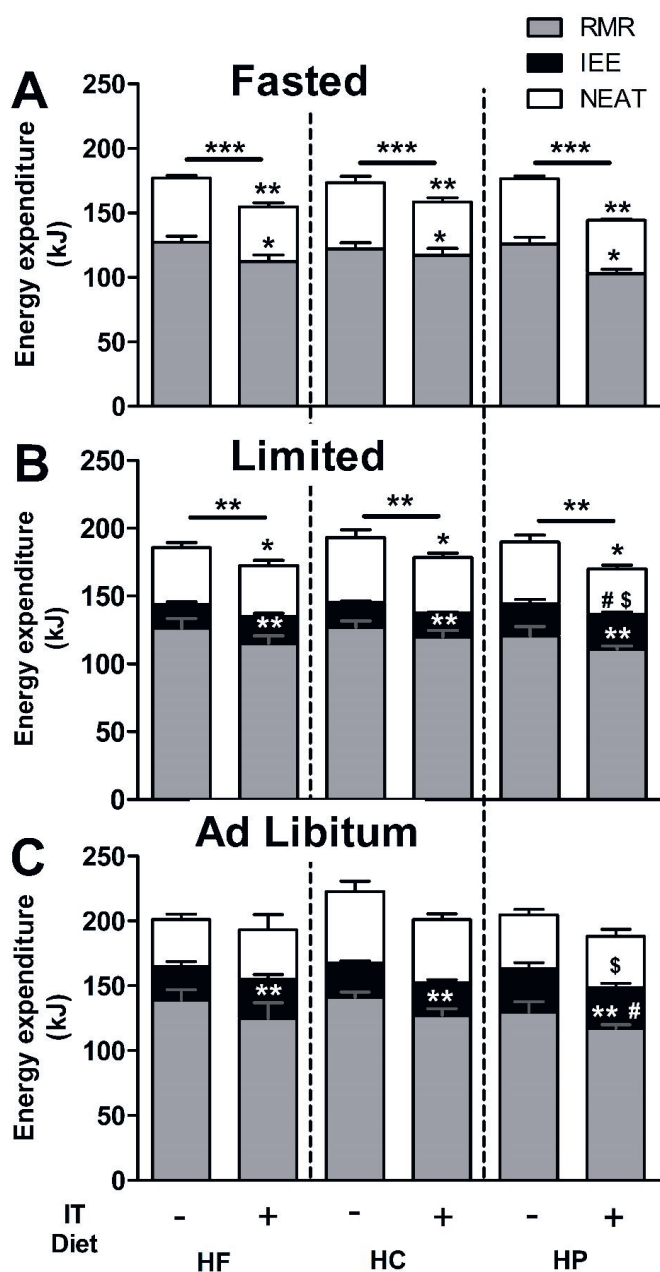


Figure 2. Daily energy expenditure (kJ) on fasting day (A), limited intake day (B), and ad libitum intake day (C). Levels of significance by IT are depicted by * ($p < 0.05$), ** ($p < 0.01$), *** ($p < 0.001$), levels of significance by diet are depicted by \$ ($p < 0.01$, for difference between HP and

HC), # ($p < 0.05$ for difference between HP and HF) and \$ ($p < 0.05$ for difference between HP and HC) after ANCOVA with LBM as covariate.

Energy budget:

On the limited intake day and ad libitum days, the difference between TEI and TEE allowed us to calculate the energy budgets. Our data revealed that energy budgets were neither affected by diet nor by surgery during the two different days (Figure 3).

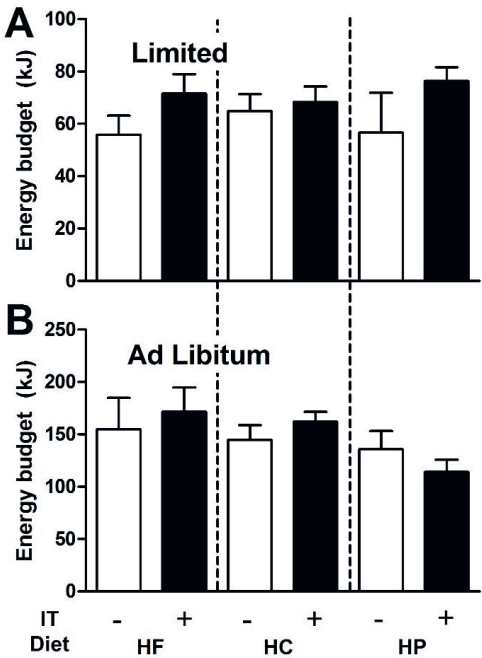


Figure 3. Energy budgets calculated on the limited intake day (A) and the ad libitum intake day (B) during indirect calorimetry.

Discussion

In the present study IT+ caused a transient body weight loss followed by partial weight regain albeit this weight regain was lower in IT+ than in IT- rats. This is a pattern that is comparable to findings in previous studies (Chelikani et al 2010, Koopmans et al 1982, Strader et al 2005,). Whereas the 30-day energy intake explained to a large extent the differences in weight regain between IT- and IT+ rats (unpublished data) with IT+ rats eating significantly less than IT- rats, our study investigated potential effects of IT on energy expenditure and energy budget when rats became weight stable following IT. We found that IT+ caused reductions in total (daily) energy expenditure under fasting, limited intake and ad libitum conditions, which persisted in the fasting and limited intake state when the levels of TEE were analyzed with L|BM as covariate. RMR was also lowest in IT+ rats under all diet conditions, and persisted when analyzed with LBM as covariate, irrespective of fasting, limited intake or ad libitum condition. When total body weight was used as a covariate, only the effect of surgery persisted in the fasting condition, and in interaction with diet, with the HP group mostly contributing to this effect. For this reason, it seems plausible that IT reduced RMR partly by the fact that IT caused weight loss and reduced mass specific metabolic rate, but on top of that there was an effect of IT per se.

Although some controversy exists on the subject (see a.o.: Faria et al 2012, Rabl et al 2014), the energy expenditure-reducing effect of IT appears to be consistent with the effects of other bariatric surgeries, where RMR either corrected for lean body weight in fasted humans (Carrasco et al 2007) or uncorrected (Liu et al 2012) was found to be reduced. RYGB surgery in humans was also shown to decrease TEE (Rabl et al 2014, Schmidt et al 2016) and vertical banded gastroplasty resulted in significantly lower daily EE and sleeping metabolic rate 12 months after surgery, with increased lipid oxidation (van Gemert et al 2000). Co-variate analysis with LBM (or other correlates of mass specific metabolic rate) is important, as it may explain some controversies in other data sets on whether or not bariatric surgeries affect metabolic rate (Bueter et al 2010, Stylopoulos et al 2009, Zheng 2009, Stefater et al 2012, Nadreau et al 2005).

In our study, LBM was not affected by diet or surgery, and may have been stable throughout the last phase (i.e., between days 30 and day of termination). Possible explanations of the metabolic adaptation seen after bariatric surgeries could be reduced activity of the sympathetic nervous system (Curry et al 2013), decreased levels of leptin (Knuth et al 2014) and/or thyroid hormones (Rosenbaum et al 2002) or increased level of PYY (McNeil 2015), that are altered by the procedure of IT, besides the effects mediated by weight loss itself. We found that IT+ rats had lower non-exercise activity (NEAT) thermogenesis (significant on fasting and limited intake days) compared to the IT- rats, which persisted when LBM was used as a co-variate. Contrasting results of bariatric surgery on NEAT are found, as for example indicated in the report of Saedi et al, where rats that underwent sleeve gastrectomy or RYGB had respectively smaller and greater levels of NEAT relative to controls (Saedi et al 2012). Lower EE and NEAT as a result of bariatric surgery as observed in our study and others (van Gemert et al 2000, Schmidt et al 2016) could have been the result of greater fatigue in reduced food intake conditions in order to conserve energy (Shibata et al 1987, Westerterp 2012). In contrast, surgery did not affect SDA, nor did it affect IEE under limited and ad libitum feeding conditions either or not analysed with LBM and/or total body weight as co-variate. IEE has been found to be increased after RYGB in humans, 3 hours after the subjects were given a standardized meal (Faria et al 2012, Wilms et al 2013) and in rats (Beuter et al 2012). Contrary to other energy expenditure components IEE was found not to decline following weight loss by traditional methods (Leibel et al 1995, Luscombe et al 2002). Diet on the other hand did affect SDA and IEE with highest levels either corrected or not for LBM found in the HP feeding rats. This is in agreement with the findings that a high protein diet (Bray et al 2012, Thearle et al 2013) can increase energy expenditure in humans (Huang et al 2013) and in rodents (Petzke et al 2007). Furthermore, a HP diet has been reported to increase diet-induced energy expenditure (i.e., which is a component of IEE) and satiety, which were positively correlated in lean women (Westerterp-Plantega et al 1999) and in healthy subjects (Westerterp et al 2004) leading to weight loss. The underlying mechanisms of higher energy expenditure after a HP meal is not clearly defined, although several potential pathways have been suggested. Liver uncoupling protein 2 (UCP2) and skeletal muscle uncoupling protein 3 (UCP3)

mRNA expression has been shown to increase after consuming high protein diet in rats (Petzke et al 2007). Consuming a HP diet may also augment fatty acid oxidation with heat dissipated resulting in a higher energy expenditure. The higher energy expenditure of rats eating a HP diet could also reflect the higher cost of protein turnover and storage (Bray et al 2015). In our study, however, we did not detect significantly higher total daily energy expenditure in HP rats.

From total energy intake and total expenditure, we calculated the energy budgets for each individual animal, and observed that neither diet nor surgery affected energy budget in this condition where rats were relatively weight stable. Had we found significant differences, we would have expected that differences in body weight between groups would either become larger or smaller. Thus, IT appears to be a well-tolerated bariatric procedure causing reductions in several components of energy expenditure, except for IEE irrespective of macronutrient composition of the diet. Maintenance of IEE in the face of limited caloric intake may be a mechanism by which animals undergoing IT fail to bridge the body weight gap that exists between IT+ and IT- rats. Feeding a HP diet may contribute as well to maintenance of this gap, as this caused the highest levels of IEE among the three macronutrient mixtures.

References

Azvolinsky A. The Obesity–Cancer Link: A Growing Connection. JNCI J Natl Cancer Inst [Internet]. 2016 Oct 12;108(10). Available from: <https://doi.org/10.1093/jnci/djw243>

Barreto SG, Soenen S, Chisholm J, Chapman I, Kow L. Does the ileal brake mechanism contribute to sustained weight loss after bariatric surgery? ANZ J Surg [Internet]. 2018 Jan 1;88(1–2):20–5. Available from: <https://doi.org/10.1111/ans.14062>

Bray GA, Smith SR, de Jonge L, Xie H, Rood J, Martin CK, et al. Effect of dietary protein content on weight gain, energy expenditure, and body composition during overeating: a randomized controlled trial. JAMA [Internet]. 2012 Jan 4;307(1):47–55. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/22215165>

Bueter M, Löwenstein C, Olbers T, Wang M, Cluny NL, Bloom SR, et al. Gastric Bypass Increases Energy Expenditure in Rats. Gastroenterology [Internet]. 2010 May 1;138(5):1845–1853.e1. Available from: <https://doi.org/10.1053/j.gastro.2009.11.012>

Butler AA, Kozak LP. A recurring problem with the analysis of energy expenditure in genetic models expressing lean and obese phenotypes. Diabetes [Internet]. 2010 Feb;59(2):323–9. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/20103710>

Carrasco F, Papapietro K, Csendes A, Salazar G, Echenique C, Lisboa C, et al. Changes in Resting Energy Expenditure and Body Composition after Weight Loss following Roux-en-Y Gastric Bypass. Vol. 17, Obesity surgery. 2007. 608–616 p.

Chelikani PK, Shah IH, Taqi E, Sigalet DL, Koopmans HH. Comparison of the effects of Roux-en-Y gastric bypass and ileal transposition surgeries on food intake, body weight, and circulating peptide YY concentrations in rats. *Obes Surg* [Internet]. 2010 Sep;20(9):1281—1288. Available from: <https://doi.org/10.1007/s11695-010-0139-6>

Curry TB, Somaraju M, Hines CN, Groenewald CB, Miles JM, Joyner MJ, et al. Sympathetic support of energy expenditure and sympathetic nervous system activity after gastric bypass surgery. *Obesity (Silver Spring)* [Internet]. 2013 Mar;21(3):480–5. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/23592656>

de Cleve R, Mota FC, Gadducci AV, Cardia L, D'Andréa Greve JM, Santo MA. Resting metabolic rate and weight loss after bariatric surgery. *Surg Obes Relat Dis* [Internet]. 2018 Jun 1;14(6):803–7. Available from: <https://doi.org/10.1016/j.soard.2018.02.026>

DeLany JP, Lovejoy JC. ENERGY EXPENDITURE. *Endocrinol Metab Clin North Am* [Internet]. 1996;25(4):831–46. Available from: <http://www.sciencedirect.com/science/article/pii/S0889852905703571>

Dixon JB, Zimmet P, Alberti KG, Rubino F, Prevention IDFT on E and. Bariatric surgery: an IDF statement for obese Type 2 diabetes. *Diabet Med* [Internet]. 2011 Jun;28(6):628–42. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/21480973>

Faria SL, Faria OP, de Almeida Cardeal M, Gouvêa HR de, Buffington C. Diet-induced thermogenesis and respiratory quotient after Roux-en-Y gastric bypass. *Surg Obes Relat Dis* [Internet]. 2012 Nov 1;8(6):797–802. Available from: <https://doi.org/10.1016/j.soard.2012.06.008>

Faria SL, Faria OP, Buffington C, de Almeida Cardeal M, Rodrigues de Gouvêa H. Energy Expenditure Before and After Roux-en-Y Gastric Bypass. *Obes Surg* [Internet]. 2012;22(9):1450–5. Available from: <https://doi.org/10.1007/s11695-012-0672-6>

Ferrannini E. The theoretical bases of indirect calorimetry: A review. *Metab - Clin Exp* [Internet]. 1988 Mar 1;37(3):287–301. Available from: [https://doi.org/10.1016/0026-0495\(88\)90110-2](https://doi.org/10.1016/0026-0495(88)90110-2)

Finkelstein EA, Trogdon JG, Cohen JW, Dietz W. Annual Medical Spending Attributable To Obesity: Payer-And Service-Specific Estimates. *Health Aff* [Internet]. 2009 Sep 1;28(5):w822–31. Available from: <https://doi.org/10.1377/hlthaff.28.5.w822>

Hall KD, Guo J. Obesity Energetics: Body Weight Regulation and the Effects of Diet Composition. *Gastroenterology* [Internet]. 2017/02/11. 2017 May;152(7):1718-1727.e3. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/28193517>

Huang X, Hancock DP, Gosby AK, McMahon AC, Solon SMC, Le Couteur DG, et al. Effects of dietary protein to carbohydrate balance on energy intake, fat storage, and heat production in mice. *Obesity* [Internet]. 2013 Jan 1;21(1):85–92. Available from: <https://doi.org/10.1002/oby.20007>

Khaylis A, Yiaslas T, Bergstrom J, Gore-Felton C. A review of efficacious technology-based weight-loss interventions: five key components. *Telemed J E Health* [Internet]. 2010 Nov;16(9):931–8. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/21091286>

Knuth ND, Johannsen DL, Tamboli RA, Marks-Shulman PA, Huizenga R, Chen KY, et al. Metabolic adaptation following massive weight loss is related to the degree of energy imbalance and changes in circulating leptin. *Obesity* (Silver Spring) [Internet].

2014/09/19. 2014 Dec;22(12):2563–9. Available from:

<https://www.ncbi.nlm.nih.gov/pubmed/25236175>

Koopmans HS, Ferri G-L, Sarson DL, Polak JM, Bloom SR. The effects of ileal transposition and jejunoileal bypass on food intake and GI hormone levels in rats. *Physiol Behav* [Internet]. 1984;33(4):601–9. Available from:

<http://www.sciencedirect.com/science/article/pii/0031938484903780>

Kraschnewski JL, Boan J, Esposito J, Sherwood NE, Lehman EB, Kephart DK, et al. Long-term weight loss maintenance in the United States. *Int J Obes (Lond)* [Internet].

2010/05/18. 2010 Nov;34(11):1644–54. Available from:

<https://www.ncbi.nlm.nih.gov/pubmed/20479763>

Leibel RL, Rosenbaum M, Hirsch J. Changes in Energy Expenditure Resulting from Altered Body Weight. *N Engl J Med* [Internet]. 1995 Mar 9;332(10):621–8. Available from: <https://doi.org/10.1056/NEJM199503093321001>

Liu X, Lagoy A, Discenza I, Silva JE, Romanelli J, Lewis E, et al. Metabolic and Neuroendocrine Responses to Roux-en-Y Gastric Bypass. I: Energy Balance, Metabolic Changes, and Fat Loss. *J Clin Endocrinol Metab* [Internet]. 2012 Aug 1;97(8):E1440–50. Available from: <https://doi.org/10.1210/jc.2012-1016>

Luscombe ND, Clifton PM, Noakes M, Parker B, Wittert G. Effects of Energy-Restricted Diets Containing Increased Protein on Weight Loss, Resting Energy Expenditure, and the Thermic Effect of Feeding in Type 2 Diabetes. *Diabetes Care* [Internet]. 2002 Apr 1;25(4):652 LP – 657. Available from:
<http://care.diabetesjournals.org/content/25/4/652.abstract>

Lusk G. *The elements of the science of nutrition*. New York: Johnson Reprint Corp., 1924; 4th ed., reprinted 1976.)

Maljaars PWJ, Peters HPF, Mela DJ, Masclee AAM. Ileal brake: A sensible food target for appetite control. A review. *Physiol Behav* [Internet]. 2008;95(3):271–81. Available from: <http://www.sciencedirect.com/science/article/pii/S0031938408002278>

Martin CK, Brock C, Covington J, Rood J, Redman LM, de Jonge L, et al. Effect of protein overfeeding on energy expenditure measured in a metabolic chamber. *Am J Clin Nutr* [Internet]. 2015 Jan 14;101(3):496–505. Available from:
<https://doi.org/10.3945/ajcn.114.091769>

Masclee AAM, Keszthelyi D, Maljaars PWJ. An ileal brake-through? *Am J Clin Nutr* [Internet]. 2010 Aug 4;92(3):467–8. Available from:
<https://doi.org/10.3945/ajcn.2010.30180>

McCue M. Specific dynamic action: A century of investigation. Vol. 144, *Comparative biochemistry and physiology. Part A, Molecular & integrative physiology*. 2006. 381–394 p.

McGuire S, Shields M., Carroll M.D., Ogden C.L. Adult Obesity Prevalence in Canada and the United States. NCHS Data Brief no. 56, Hyattsville, MD: National Center for Health Statistics, 2011. Adv Nutr [Internet]. 2011 Jun 28;2(4):368–9. Available from: <https://doi.org/10.3945/an.111.000497>

McNeil J, Doucet É, Schwartz A, Rabasa-Lhoret R, Lavoie J-M, Brochu M. Changes in Leptin and Peptide YY Do Not Explain the Greater-Than-Predicted Decreases in Resting Energy Expenditure After Weight Loss. J Clin Endocrinol Metab [Internet]. 2015 Mar 1;100(3):E443–52. Available from: <https://doi.org/10.1210/jc.2014-2210>

Mirahmadian M, Hasani M, Taheri E, Qorbani M, Hosseini S. Influence of gastric bypass surgery on resting energy expenditure, body composition, physical activity, and thyroid hormones in morbidly obese patients. Diabetes Metab Syndr Obes [Internet]. 2018 Oct 23;11:667–72. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/30425544>

Miras AD, le Roux CW. Mechanisms underlying weight loss after bariatric surgery. Nat Rev Gastroenterol & Hepatol [Internet]. 2013 Jul 9;10:575. Available from: <https://doi.org/10.1038/nrgastro.2013.119>

Moehlecke M, Trindade MRM, Mazzuca AC, Blume CA, Rheinheimer J, Leitão CB. Energy expenditure changes after Roux-en-Y Gastric Bypass. Diabetes Metab Syndr [Internet]. 2015 Nov 11;7(Suppl 1):A240–A240. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4659224/>

Nadreau E, Baraboi E-D, Samson P, Blouin A, Hould F-S, Marceau P, et al. Effects of the biliopancreatic diversion on energy balance in the rat. *Int J Obes* [Internet]. 2005 Nov 22;30:419. Available from: <https://doi.org/10.1038/sj.ijo.0803166>

Petzke KJ, Riese C, Klaus S. Short-term, increasing dietary protein and fat moderately affect energy expenditure, substrate oxidation and uncoupling protein gene expression in rats. *J Nutr Biochem* [Internet]. 2007;18(6):400–7. Available from: <http://www.sciencedirect.com/science/article/pii/S0955286306001860>

Rabl C, Rao MN, Schwarz J-M, Mulligan K, Campos GM. Thermogenic changes after gastric bypass, adjustable gastric banding or diet alone. *Surgery* [Internet]. 2014 Oct;156(4):806–12. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/25239323>

Ramzy AR, Nausheen S, Chelikani PK. Ileal transposition surgery produces ileal length-dependent changes in food intake, body weight, gut hormones and glucose metabolism in rats. *Int J Obes* [Internet]. 2013 Oct 29;38:379. Available from: <https://doi.org/10.1038/ijo.2013.201>

Saeidi N, Nestoridi E, Kucharczyk J, Uygun MK, Yarmush ML, Stylopoulos N. Sleeve gastrectomy and Roux-en-Y gastric bypass exhibit differential effects on food preferences, nutrient absorption and energy expenditure in obese rats. *Int J Obes (Lond)* [Internet]. 2012/10/09. 2012 Nov;36(11):1396–402. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/23044855>

Schmidt JB, Pedersen SD, Gregersen NT, Vestergaard L, Nielsen MS, Ritz C, et al. Effects of RYGB on energy expenditure, appetite and glycaemic control: a randomized

controlled clinical trial. *Int J Obes* [Internet]. 2015 Aug 25;40:281. Available from: <https://doi.org/10.1038/ijo.2015.162>

Shibata H, Bukowiecki LJ. Regulatory alterations of daily energy expenditure induced by fasting or overfeeding in unrestrained rats. *J Appl Physiol* [Internet]. 1987 Aug 1;63(2):465–70. Available from: <https://doi.org/10.1152/jappl.1987.63.2.465>

Somogyi E, Hoornenborg CW, Bruggink JE, Nyakas C, van Beek AP, van Dijk G. Ileal transposition; a non-restrictive bariatric surgical procedure that reduces body fat and increases ingestion-related energy expenditure Submitted to *Physiology and Behavior* 2019

Stefater MA, Wilson-Pérez HE, Chambers AP, Sandoval DA, Seeley RJ. All bariatric surgeries are not created equal: insights from mechanistic comparisons. *Endocr Rev* [Internet]. 2012/05/01. 2012 Aug;33(4):595–622. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/22550271>

Strader AD, Vahl TP, Jandacek RJ, Woods SC, D'Alessio DA, Seeley RJ. Weight loss through ileal transposition is accompanied by increased ileal hormone secretion and synthesis in rats. *Am J Physiol Metab* [Internet]. 2005 Feb 1;288(2):E447–53. Available from: <https://doi.org/10.1152/ajpendo.00153.2004>

Tamboli RA, Hossain HA, Marks PA, Eckhauser AW, Rathmacher JA, Phillips SE, et al. Body composition and energy metabolism following Roux-en-Y gastric bypass surgery. *Obesity* (Silver Spring) [Internet]. 2010/04/22. 2010 Sep;18(9):1718–24. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/20414197>

Thearle MS, Pannacciulli N, Bonfiglio S, Pacak K, Krakoff J. Extent and determinants of thermogenic responses to 24 hours of fasting, energy balance, and five different overfeeding diets in humans. *J Clin Endocrinol Metab* [Internet]. 2013/05/10. 2013 Jul;98(7):2791–9. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/23666976>

Thivel D, Brakonietki K, Duche P, Morio B, Boirie Y, Laferrère B. Surgical weight loss: impact on energy expenditure. *Obes Surg* [Internet]. 2013 Feb;23(2):255–66. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/23224568>

van Gemert WG, Westerterp KR, van Acker BA, Wagenmakers AJ, Halliday D, Greve JM, et al. Energy, substrate and protein metabolism in morbid obesity before, during and after massive weight loss. *Int J Obes Relat Metab Disord*. 2000 Jun;24(6):711–8.

Weiss EC, Galuska DA, Kettel Khan L, Gillespie C, Serdula MK. Weight Regain in U.S. Adults Who Experienced Substantial Weight Loss, 1999–2013. *Am J Prev Med* [Internet]. 2007 Jul 1;33(1):34–40. Available from: <https://doi.org/10.1016/j.amepre.2007.02.040>

Westerterp KR. Diet induced thermogenesis. *Nutr Metab (Lond)* [Internet]. 2004;1(1):5. Available from: <https://doi.org/10.1186/1743-7075-1-5>

Westerterp KR. Metabolic adaptations to over—and underfeeding—still a matter of debate? *Eur J Clin Nutr* [Internet]. 2012 Dec 12;67:443. Available from: <https://doi.org/10.1038/ejcn.2012.187>

Westerterp-Plantenga M, Rolland V, A J Wilson S, Westerterp K. Satiety related to 24 h diet-induced thermogenesis during high protein/carbohydrate vs high fat diets measured in a respiration chamber. Vol. 53, European journal of clinical nutrition. 1999. 495–502 p.

Wilms B, Ernst B, Thurnheer M, Schultes B, Schmid SM. Enhanced Thermic Effect of Food After Roux-en-Y Gastric Bypass Surgery. J Clin Endocrinol Metab [Internet]. 2013 Sep 1;98(9):3776–84. Available from: <https://doi.org/10.1210/jc.2013-1087>

Zheng H, Shin AC, Lenard NR, Townsend RL, Patterson LM, Sigalet DL, et al. Meal patterns, satiety, and food choice in a rat model of Roux-en-Y gastric bypass surgery. Am J Physiol Regul Integr Comp Physiol [Internet]. 2009/09/02. 2009 Nov;297(5):R1273–82. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/19726714>

